REMARKS

Claims 9-12 are all of the claims pending in the application.

Support for new Claim 9 may be found as follows. The preamble is based in part on the preamble of original Claim 7. Support for step (a) of Claim 9 may be found on page 14, lines 7-14 of the present specification. Support for step (b) of Claim 9 may be found on page 16, line 21 to page 17, line 7 of the present specification for "whole bone marrow cells," since the procedure disclosed does not fractionate the bone marrow obtained from the femurs and tibias of the experimental BALB/c mice. Further support for the "hepatic portal venous administration" of step (b) of Claim 9 may be found on page 17, lines 8-14 of the present specification. Applicants respectfully submit that in the previous Office Action, the Examiner requested that the term "portal" be further defined as "hepatic portal" in the claims. Applicants have done so in the new claims here. Finally, support for "intravenous administration" may be found on page 17, lines 15-20 of the present specification.

Support for new Claim 10 may be found on page 29, lines 7-16 of the present specification.

Support for new Claim 11 may be found on page 26, line 17 to page 27, line 1 of the present specification.

Support for new Claim 12 may be found on page 28, lines 22-25 of the present specification.

Hence, Applicants respectfully submit that no new matter has been introduced and respectfully requests entry of new Claims 9-12.

On page 2 of the Office Action, the Examiner requests that the specification be amended to include reference to the priority information for the PCT application.

Applicants have amended the specification to make such a reference. Hence, Applicants respectfully submit that the Examiner's request has been satisfied.

In paragraph 1, on page 2 of the Office Action, the Examiner rejects Claims 1-2, 5-6 and 8 under 35 U.S.C. § 112, second paragraph, as being indefinite.

Specifically, the Examiner states that Claims 1-2 and 5-6 are indefinite in the recitation of "portal", as the term has multiple meanings in medical usage which can broadly read upon any gateway or entrance including, for example, a "portal" for medicament addition of an intravenous "drip" apparatus. Hence, the Examiner points out that if Applicants' intent is the "hepatic portal" vein, then this should be more clearly conveyed in the claims.

Also, the Examiner states that Claim 8 recites the use of a tolerogen comprising hematopoietic stem cells, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process Applicants are intending to encompass since a claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Applicants have canceled Claims 1-8, thus rendering moot the Examiner's rejection. Applicants have added new Claims 9-12 to clarify the present claimed invention. Support for new Claims 9-12 are indicated above. Hence, Applicants respectfully submit that the rejection has been overcome.

In paragraph 2, on page 2 of the Office Action, the Examiner rejects Claim 8 under 35 U.S.C. § 101 because the claimed recitation of use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101.

Applicants have canceled Claim 8, thereby rendering this rejection moot.

In paragraph 3, on page 3 of the Office Action, the Examiner rejects Claims 1-6 and 8 under 35 U.S.C. § 102(b) as being anticipated by Zhang et al.

Specifically, the Examiner states that Zhang et al teaches the administration to a subject of a first composition comprising allogeneic bone marrow cells enriched for hematopoietic stem cells via the recipients hepatic portal vein. The Examiner further notes that Zhang et al teaches the intravenous administration of allogeneic bone marrow cells enriched for hematopoietic stem cells to the same subjects and further teaches that this protocol resulted in a tolerant state which persisted more than 49 days. The Examiner asserts that Zhang et al also teaches that injection of bone marrow cells via the hepatic portal vein suppresses donor-specific rejection and that

administration of donor antigens via the hepatic portal vein results in the increased survival of cardiac and renal grafts, i.e., graft tolerance.

Further, the Examiner notes that Claims 3 and 4 are included in this rejection because the composition is not altered by its intended use with radiotherapy and is the same as the composition taught by Zhang et al. Further, the Examiner notes that Claim 8 is included in the rejection because it is a "use" claim which recites no positive steps and therefore can read upon the composition being used as well as any method "using" said composition.

Applicants have canceled Claims 1-8, thus rendering moot the Examiner's rejection. Applicants have added new Claims 9-12 to clarify the present claimed invention.

Further, Applicants respectfully submit that Zhang et al teaches that portal venous (p.v.) injection plus intravenous (i.v.) injection alone are effective to induce tolerance. However, Applicants submit that Zhang et al does not disclose the irradiation of a recipient, and therefore does not teach or suggest a method step comprising irradiation of the recipient, followed by hepatic portal venous administration or intravenous administration of whole bone marrow cells a presently claimed. Applicants note that the Examiner did not reject original method Claim 7 in view of Zhang et al. Hence, the Examiner implicitly acknowledges that the step of subjecting a patient to radiation is not taught in Zhang et al.

Applicants submit that Zhang et al teaches that tolerance was maintained for more than 49 days by p.v. injection plus i.v. injection (see page 1563, left column, first paragraph and Figure 10). However, Applicants have found that employing the method of Zhang et al of p.v. plus i.v. administration without irradiation, embodied in Test Group 3, found on page 20, lines 17-22 of the present specification, shows that immunotolerance was maintained for less than 36 weeks (see Table 1 on page 19, of the present specification). Specifically, in Test Group 3, Table 1 shows that engraftment of the transferred skin was found only in 4 of 6 mice (engraftment rate: 67%) at week 36 after transplantation.

In contrast, Applicants respectfully submit that Test Example 4 beginning on page 25, line 18 of the present specification, demonstrates that the engraftment rate was 100% for at least 36 weeks, when tolerance was induced by a method according to the present claimed invention

which comprises irradiation of a recipient using a sublethal radiation dose of at least 6.5 Gy, followed by hepatic portal venous administration or intravenous administration (see the data for Group II in Figure 2 and the explanation on page 29, line 22 to page 30, line 18).

Further, Applicants respectfully submit that in Group I, which received a radiation dose of 6.5 Gy in association with portal administration of bone marrow cells (see page 29, lines 6-9 of the present specification), the engraftment rate was 100% at week 23 (see Figure 2). Applicants have confirmed that Group I mice, engraftment was maintained until the test animals died from senility.

Moreover, in Group III, which was given a radiation dose of 6.5 Gy and intravenous administration, engraftment was maintained in 6 of 7 mice (see page 29, lines 13-16 of the present specification). In the 6 mice, engraftment was maintained until the mice died from senility.

Therefore, in view of the above data, Applicants respectfully submit that Zhang et al does not anticipate the present claimed method, wherein specific irradiation treatment is carried out in combination with hepatic portal venous administration or intravenous administration. Further, one skilled in the art would not have expected that the claimed combination would have achieved a high engraftment rate, and thus Zhang et al does not render obvious the present claimed method. Thus, Applicants respectfully request withdrawal of this rejection.

In paragraph 4, on page 3 of the Office Action, the Examiner rejects Claims 1-4 and 7-8 under 35 U.S.C. § 102(b) as being anticipated by Orloff et al.

Specifically, the Examiner states that Orloff et al teaches (1) a method for inducing specific allogeneic tolerance to a transplanted organ; (2) lethal irradiation of host animals followed by their reconstruction with T cell depleted allogeneic bone marrow cells; (3) treatment which results in the establishment of hematopoietic chimerism; and (4) transplantation of small bowel to the chimeric animals. According to the Examiner, graft survival in chimeric animals ranged from more than 135 to more than 304 days with no signs of rejection in any animals which compares to a median graft survival of only 8 days in control animals.

Further, the Examiner notes that Claims 1 and 2 are included in this rejection because the composition is not altered by its intended use with portal administration and is the same as the composition taught by Orloff et al.

Applicants canceled Claims 1-8, thereby rendering moot this rejection.

With respect to new Claims 9-12, Applicants submit that Orloff et al teaches irradiating a recipient with a lethal dose of 10.5 Gy and then intravenously administering a mixture of T cell-depleted bone marrow cells derived from a donor and a host to establish mixed hematopoietic chimerism. Then, 30 days after intravenous administration, Orloff et al transplants a small bowel to the chimeric recipient (see "Methods" on page 222 and "Bone Marrow Transplantation" on page 223, right column).

Applicants respectfully submit that the present claimed method differs from that taught in Orloff et al since the present claimed method employs the steps of (a) a radiation treatment carried out using a sublethal radiation dose, and (b) then administering whole bone marrow cells from a graft donor to establish fully allogeneic chimeras.

Applicants respectfully submit that Orloff et al does not teach or suggest the claimed combination of the sublethal radiation treatment and the administration of whole bone marrow cells.

Further, Applicants submit that the present claimed method achieves an engraftment rate of approximately 100% when the transplantation is performed within the same day as the bone marrow cell administration, as embodied in Test Example 4 and results shown in Figure 2 (see new Claim 12). Applicants submit that the one day protocol is highly advantageous since it enables organ transplantation from a donor suffering from brain death, a condition in which a patient has a total cessation of brain function for 24 hours. In contrast, Applicants submit that transplantation from such a donor cannot be carried out by the method of Orloff et al, which teaches that the organ transplantation step is performed 30 days after the bone marrow cell administration (see page 223, right column, in "Bone Marrow Transplantation" section of Orloff et al).

Therefore, Applicants respectfully submit that the present claimed invention is not anticipated or rendered obvious by Orloff et al.

In paragraph 5, on page 4 of the Office Action, the Examiner rejects Claims 1-4 and 7-8 under 35 U.S.C. § 102(b) as being anticipated by Sharabi et al.

Specifically, the Examiner states that Sharabi et al teaches (1) a method for the induction of specific tolerance to a transplanted xenogeneic organ; (2) whole body irradiation of a subject animal followed by infusion of T cell depleted xenogeneic bone marrow cells; and (3) that donor type xenogeneic skin grafts placed 4 months after bone marrow transplantation were accepted, while skin grafts allogeneic to the donor were rapidly rejected.

Applicants canceled Claims 1-8, thereby rendering moot this rejection.

With respect to new Claims 9-12, Applicants submit that Sharabi et al teaches a method of inducing immunological tolerance for organ transplantation by: (a) pretreating recipient mice with monoclonal antibodies against NK1.1, Thy-1, 2, CD4 and CD8, (a necessary step in Sharabi's method, see page 196, right column, first full paragraph), (b) irradiating the thymus with a 7 Gy dose which is carried out after 3 Gy whole body radiation, (c) intravenously administering T-cell depleted bone marrow cells; and (d) waiting 4 months before transplanting rat skin grafts onto the recipient mice.

Applicants submit that Sharabi et al does not teach or suggest the present claimed method of administering whole bone marrow cells or performing the organ transplantation within one day of administering whole bone marrow cells.

Further, the method of Sharabi et al resulted in the rejection of skin grafts within 100 days in 2 out of 6 mice, as shown in Table 2 on page 199 and Figure 4 on page 200 of Sharabi et al. Thus, the present claimed method induces remarkable immunological tolerance unexpected from the disclosure of Sharabi et al. To provide further support of the unexpected results achieved by the present invention, Applicants submit herewith two papers co-authored by Mr. Ikehata, one of the co-inventors of the present invention (Kushida et al, *Blood*, 95(5):1862-1868 (March 1, 2000); and Takeuchi et al, *Blood*, 91(12):4616-4623 (June 15, 1998)). These papers compare the method of Sharabi et al and the present claimed

method and demonstrate that depletion of CD4+ T-cells and CD8+ T-cells, employed by the method of Sharabi et al, does not lead to a high survival rate (see page 1863, "Materials and Methods," left column Kushida et al and page 1866 of Kushida et al, left column, first paragraph; see also page 4616 Abstract, right column, and page 4617 "Materials and Methods," left column, and Figure 2 of Takeuchi et al).

Therefore, Applicants respectfully submit that the present claimed invention is not anticipated or rendered obvious by Sharabi et al.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

Page 1, after the title and before line 1,

-- This application is a §371 of PCT/JP98/00909, filed on March 4, 1998. --

is being inserted.

IN THE CLAIMS:

Claims 1-8 are canceled.

Claims 9-12 are being added as new claims.